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# ' ROLE OF ENDOTOXINS AND BILE ACIDS IN THE PATHOGENESIS OF SEPTIC CIRCULATORY SHOCK

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It is well known that the bacterial endotoxins play an important role in he pathogenesis of irreversible septic (surgical) shock. The endotoxins can initiate the production of noxious mediators (e.g. cytokines, prostaglandins etc.) and these factors are the elicitors of the endotoxic shock.

It has long been also known that the toxic effects of endotoxic lipopolysaccharides (LPS) under experimental conditions can be induced only when they are administered parenterally. However, in naturaEy occurring enteroendotoxemic diseases (e.g. various shocks, etc.), the LPS absorb from the intestinal tract. The parenterally (intraperitoneal or intravenous) administered LPS induces prostration, diarrhea, and circulatoiy disturbances indistinguishable from those observed in natural diseases. At autopsy, animals killed by parenterally administered LPS show changes that are similar to the natural diseases of species sensitive to LPS (intestinal edema, hemorrhages, etc.). The generally used experimental models differ from natural diseases only in the mode by which LPS enters the blood circulation *(2,7)*. Given orally, LPS has no effect, even on sensitive species, when given in doses from 500 to 3.000 time the minimal parenterally lethal dosage.lt is also ineffective when the intestinal mucosa of the experimental animal has been damaged by various interventions. There is no in vitro evidence of the existence of some intestinal enzyme which could specifically decompose the LPS and thus produce resistance to the orally administered material. As a matter of fact, orally administered LPS can be recovered essentially unaltered from the gastrointestinal tract by means of the phenol-water extraction procedure. Even in a lead acetate sensitizing procedure, orally administered LPS has not been found to be toxic. The way in which LPS reaches the circulation from the intestinal tract in natural endotoxic diseases remains a mystery.

The first clue to the explanation for resistance to orally administered LPS was the demonstration that its treatment in vitro with sodium deoxycholate resulted in detoxification due to fragmentation of the LPS molecules. This process is completely reversible when the sodium deoxycholate is removed by dialysis ***(8).*** These studies suggested to us that bile acids in vivo might be significant in the inactivation ofLPS.

On the basis of the above-mentioned results, we wanted to demonstrate the in vivo role of bile in the absorption and detoxification ofLPS. For this purpose the common bile ducts of rats were chronically cannulated. In the bile-deprived rats a significant amount of perorally adminstered LPS was absorbed from the intestinal canal into the blood. Absorption was demonstrated by the lethal effect of LPS previously hypersensitized by lead acetate and by radioactivities found in blood samples. In addition, the presence of active LPS was also demonstrated biologically by the administration of the sera to other rats made hypersensitive to LPS with lead acetate. The intestinal absoiption ofLPS in rats deprived of bile can be prevented by sodium deoxycholate, or bile protected the majority of animals

against the lethal effect of LPS. These in vivo experiments demonstrated that the physiological surfactants, the bile acids, play an important role in the gastrointestinal tract in relation to the toxic properties of bacterial LPS. Provided that the rats were made bile deficient by the chronic cannulation of their common bile duct, the absorption of perorally administered LPS from the intestinal tract into the blood could be provoked in a quantity that was sufficient to elicit a typical endotoxin shock experimental enteroendotoxemia. However, these experiments demonstrated the protective effect of bile acids against the experimental enteroendotoxemia *(7)*.

These findings were confirmed by other methods. It was demonstrated in rats (with lead acetate hypersensitization) that the absence of bile salts in the intestinal tract in obstructive jaundice (induced by ligation of bile duct) allows perorally given LPS to be. absorbed and that this absorption can be prevented by the oral administration of bile salts ***(1,6).*** Endotoxemia was also demonstrated with the Limulus test in human patients with renal failure in obstructive jaundice (J). These findings suggest that bile acids play an important role in the defense mechanism of the macroorganism against bacterial LPS *(2,3)*. However, the mechanism of LPS absorption from the gastrointestinal tract of bile-deficient rats requires further elucidation.

In another experiment the "antiendotoxic" effect of various detergents (sodium lauryl sulfate, acetylammonium bromide, benzalkonium chloride, Tween 20, polyoxyethylene sorbitan monolaurate) were tested, but only one of them (sodium lauiyl sulfate) showed a sufficient effect *(3)*. Probably the antiendotoxic effect of polymixin B sulfate is also based on its detergent property *(4)*.

All studies indicate that the intestinal detoxification of LPS is primarily due to the detergent effect of bile acids.

The role of bile in detoxification of LPS was also demonstrated in the experimental intestinal ischemica induced by the superior mesenteric arterial occlusion (SMAO). The SMAO is also an enteroendotoxemia *(9)*. If the rats were deprived of bile by the chronic cannulation of the common bile duct, the lethality of SMAO increased, because the detoxification of LPS in the intestinal tract was insufficient. Namely, the SMAO produces some significant decrease in bile acid production of rats (5).

On the other hand, with bile preparation pretreatment the lethality of SMAO could be prevented in the majority (70 %) of dogs. This finding may be a good possibility for prevention of the development of fatal intestinal ischemec shock of humans after the revascularization of SMAO *(3)*. It is worth mentioning that the administration of bile acids into the loop terminal ileum in the strangulated ileus of rats resulted about a 50 % longer survival time as compared to the control group. This result is explained by the antiendotoxic (detergent) effect of bile acids *(3)*.

Moreover, it is reasonable to suggest that this phenomenon may have a more general application because the detergent effect of bile acids was shown not to be confined to protection against bacterial LPS. A similar destructive detergent action might well be a significant factor in the natural resistance against potential toxins or infectious agents with a lipoprotein or lipid outer structure. Thus, certain viruses (e.g. the herpes group) which have a lipoprotein envelope are sensitive to the detergent action of bile acids. This defense mechanism of macrorganisms based on the detergent activity of bile acids is called the physico-chemical defence ***(2,3).***

On the basis of a few preliminary experiments, it is supposed that the sensitivity and resistance of different species to endotoxin may be correlated with the bile acid composition of their bile *(3)*.

It may also be that bile acids are significant factors in bacterial LPS detoxification in the liver as well as the intestines. It is quite likely that the endotoxin hypersensitivity induced by lead acetate is due to some alteration of the detergent effect of the bile acids. Namely, the liver homogenate of lead acetate treated rats cannot detoxify the LPS. This hypothesis may serve as an explantion of lead acetate-induced hypersensitivity.

Finally, it is also worthy of note that in the natural disorders an insufficient production of cholecystokinine (CCK) could be the cause of bile dificiency and consequence of LPS absorption/translocation. It is well known that the CCK is produced in the wall of small intestine and via blood circulation can bound to the special receptros on the gall bladder and can produced the contraction of it. If the CCK production is insufficient the bile can not evacuate into intestinal canal. So the detergent effect of bile acids can not act on the LPS molecule. In this case the LPS can translocate - in toxic form - from the intestinal tract to the blood circulation.

## *REFERENCES*

1. Bailey, M.E.: Endotoxin, bile salts and renal function in obstructive jaundice. Brit.J.Surg. 63:774,1976

2. Bertok, L.: Physioc-chemical defense of vertebrate organisms: the role of bil acids in defense against bacterial endotoxin. Perspect.Biol.Med. 21:70, 1977

3. Bertok, L.: Bacterial endotoxins and nonspecific resistance. In: Traumatic injury. Infection and other immunologic saequelae. ed. Ninnemann, J.L.University Park Press, Baltimore, MD, 1983.p. 119.

4. Corrigan, J. J. and Kiernat, J.F.: Effect of polymyxin B on endotoxin activity in a gram-negative septicemia model. Pediatr.Res. 13:48, 1979

5. Karika, Gy., Bertok, L. and Kisida, E.: Effect of bile deficiency on the survival of rats in experimental superior mesenteric arteiy occlusion (in Hungarian). Magy.Sebesz. 31:164, 1978.

6. Kisida, E., Hegediis, Z., Bertok, L. and Szentleleki, K.: Postoperativ hepatorenal syndroma kivedese epesav adagolassal. Magy.Sebesz. 49:1, 1996

7. Kocsar, L., Bertok, L. and Varteresz, V.: Effect of bile acids on the intestinal absorption of endotoxin in rats. J.Bacteriol. 100:220, 1969

8. Rudbach, J.A., Anacker, R.L., Haskins, W.T., Johnson, A.G., Milner, K.C. and Ribi, C.: Physical aspects of reversible inactivation of endotoxin. Ann.N.Y.Acad.Sci. 133:629,1966

9. Sofalvi, A., Bertok, L., Kisida, E. and Karika, Gy.: Local Shwartzman phenomenon provoked by superior mesenteric artery occlusion in rabbits (in Hungarian). Kiserl. Orvostud. 29:613,1977

## SUMMARY

**It has long been known that the toxic effects of endotoxins under experimental conditions can be induced only when they are administered parenterally. However, in naturally occuring enteroendotoxemic diseases (e.g. septic and intestinal ischemic shocks) the endotoxins, - which are produced by gram negative members of intestinal flora, - absorb from the intestinal tract to the blood circulation and can elicit pathological processes. It is an important distinction between natural and experimental endotoxin shock. If the common bile duct of rats were chronically cannulated a significant amount of perorally administered endotoxin was absorbed into the blood. This endotoxin shock can be prevented by bile acids. The physiological surfactants, the bile acids, are important facts in the defense of macroorganisms against endotoxins (physico-chemical defense). The production and passage of bile acids depend from the function of liver and the cholecystokinine (CCK) synthesis of small intestine wall. If the bile (bile acid) content of the intestinal canal decreases the endotoxin can translocate to the body and elicits toxic symptoms. So most important parts of defense against endotoxins in natural conditions are the CCK and bile acids. The consequence of damage of liver (place of bile acid synthesis) or small intestine (place of CCK synthesis) is the absorption of endotoxins.**